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# Dyslipidemia and Dietary Modification in Chilean Renal Pediatric Transplantation

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RENAL transplantation has significantly improved patient prognosis in chronic renal failure. However, increasing attention is drawn to the high incidence of cardiovascular morbidity and mortality in renal transplant recipients.[1] Persistent hypercholesterolemia of adults posttransplant is a risk factor for accelerated atherosclerosis and a 10% incidence of ischemic heart disease at 3-year follow up was observed. In both the European transplant and in the USRDS registry, cardiovascular disease is the most common cause of death posttransplantation.[2] The reason may be the accumulation of risk factors such as hypertension and dyslipidemia. Hypetriglyceridemia and hypercholesterolemia posttransplant have been described widely in the adult literature and sporadically in pediatric transplant studies.

Since the initiation of NAPRTCS, several changes in the practice patterns for donors have been observed. These changes have improved 1-year graft survival of transplant, so that most recent data show cadaveric donor graft survival in 1996 to be as good as living donor graft survival was in 1987. The survival for recipients of living donor organs has increased from 88% in 1987 to 93% in 1996.[3] The estimated half-life of the allograft is approximately 10 years; therefore, it is necessary to prevent lipid alterations at an early age in renal pediatric transplant recipients to ensure a reasonable chance of long-term survival in adult life through dietetic therapy or hypolipemic agents.

Contributing factors to posttransplant dyslipidemia include renal dysfunction, proteinuria, pretransplant dialysis, immunosuppressive therapy with corticosteroids,[4] cyclosporine,[5] beta-adrenergic antagonist, or combinations of these factors.

The impact of dyslipidemia on long-term graft and patient survival in renal transplant recipients is generally accepted. The influence of immunosuppressive drugs is clearly implicated in maintaining hypetriglyceridemia and in the development of hypercholesterolemia posttransplant.[2,6,7]

Dietary intervention remains as a cornerstone in the prevention and treatment of the hyperlipidemia. The American Heart Association (AHA) and National Cholesterol Education Program (NCEP) have provided guidelines for the treatment of hyperlipidemic patients, including the Step II Diet.[8,9] When this approach fails, pharmacologic therapy should be considered. In adult patients, diet caused modest reductions in total cholesterol and LDL-C; HMG-CoA reductase inhibitors caused the greatest and most consistent reductions in cholesterol and LDL-C.

The purpose of this study was to characterize the Chilean renal transplant population in respect to lipid profile. We tested whether an easily reproducible diet such as the AHA Step II Diet would be effective in lowering cholesterol levels in hyperlipidemic renal transplant recipients.

## PATIENTS AND METHODS

### Study Population

The study population included 42 Chilean pediatric renal transplant recipients from public health hospitals, with the same immunosuppressive posttransplant protocol according to the Chilean Pediatric Nephrology Branch recommendations. The inclusion criteria were successful renal graft for at least 4 months of stable immunosuppressive therapy, no hypolipemic or insulin therapy, and aged 6 to 20 years. Patients who met all study criteria provided written informed consent as approved by the institutional Investigation and Ethical Committee. The following information was recorded: family history of atherosclerosis or dyslipidemia; nutritional status according to body mass index (BMI) by age, sex, and Tanner stage; dietary intake; glomerular rate filtration (GRF); blood pressure; and immunosuppressive therapy.

### Collection of Serum and Diet Instructions

Fasting plasma lipid profile was obtained after a 12-hour overnight fast. Blood samples were drawn into EDTA tubes for the analysis of lipid and lipoproteins and isolated by preparative ultracentrifugation and determined enzymatically (Boehringer Mannheim, Germany). LDL cholesterol was calculated according to the Friedwald formula. The threshold serum total cholesterol and LDL cholesterol concentrations above which diet therapy should be initiated,

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**Table 1. Threshold Serum Total and Low-Density Lipoprotein Cholesterol Concentrations for the Initiation of Dietary Modification According to NCEP**

| Category | Total Cholesterol (mg/dL) | LDL-C (mg/dL) |
|---|---|---|
| Acceptable | <170 | <110 |
| Risk | 170–199 | 110–129 |
| High | ≥200 | ≥130 |

NCEP, National Cholesterol Education Program.

as well as the goals of therapy, have been defined by NCEP. Acceptable values of TC and LDL-C were considered below 75 percentiles, risk between 75 and 95 percentiles, and high above 95 percentiles[9] (Table 1).

Hypercholesterolemic patients were invited to participate in the diet and lipid profile was obtained at the beginning, 4 and 12 weeks after diet was started. Patients who accepted the diet were instructed in the AHA Step II Diet, which contains no more than 30% of total calories from fat, less than 7% of calories from saturated fatty acid with 10% polyunsaturated acid. They maintained this diet for 12 weeks. Daily cholesterol intake was limited to less than 200 mg. Total calories were prescribed according to height and sex. Dietary histories were obtained during diet instruction and compliance was assessed at every month by a 3-day recall questionnaire that has been recommended for investigations of actual nutrient intake. During the study period patients were sent recipe suggestions as well as dietary information, and were contacted by telephone on multiple occasions by the nutritionist to encourage compliance.

GRF was estimated from serum creatinine according to the Schwartz formula, which has proven to be fairly accurate in predicting GFR when renal function is normal or mildly impaired.[10] Patients received one of the following maintenance immunosuppressive regimens: prednisone diary, azathioprine, cyclosporine ($n = 23$) and prednisone alternate day, azathioprine and cyclosporine ($n = 19$). Hypertension was defined as systolic and diastolic blood pressure above 95 percentiles to sex and height according to the Task Force Report.[11]

### Statistical Analysis

Data are presented as mean and standard deviation or median and range when variables did not present a normal distribution. Student's $t$ test was performed for independent samples of homogeneous variables. Variables that did not meet this requirement were analyzed by the parametric Mann-Whitney test. Multiple regression analysis was used to establish a correlation between independent and dependent variables and chi-square test for the comparison of proportions. Fisher's exact test was used when the requirement of the minimum size to apply the chi-square method was fulfilled, and McNemar was used for the analysis of the changes that a subject experimented before and after the intervention. Paired $t$ test was applied for the differences in means of lipids concentrations before and after the diet intervention. Correlation analysis was performed to study two continue variables simultaneously, through quotient of Pearson correlation. Analysis of variance (ANOVA) for the comparison of more than two groups with homogeneous variables. For the comparison of variables that did not fulfill with this requirement we used the Kruskal-Wallis test. A $P$ value less than .05 was considered significant. The statistical analysis of the information was done using the programs of Excel 5.0. Statistica for Window 4.5, Epi Info 6.0, and S.A.S. 1980 (Statistical Analysis System).

**Table 2. Demographic Characteristics of Study Population**

| | |
|---|---|
| Patients (*N*) | 42 |
| M/F | 21/21 |
| Age (y) | 12.7 (6–20) |
| Tanner | I: 20 (51%) II–IV: 14 (36%) V: 8 (13%) |
| BMI | Normal: 50% Obese: 38% Overweight: 12% |
| T/E (Z score) | −2 ± 1.5 DE |
| Posttransplant (years) | 2.7 (0.6–8.4) |
| Prednisone/daily | 0.14 ± 0.12 (0.08–0.7 mg/kg) |
| Prednisone (alternate days) | 0.21 ± 0.08 (0.11–0.4 mg/kg) |
| Cyclosporin (doses) | 5.5 ± 1.6 (2.9–8.7 mg/k/d) |
| Cyclosporin (levels) | 167.85 ± 53 (70–278 μg/mL) |

## RESULTS

Demographic characteristics of 42 patients aged 6 to 20 years (mean 12.7), 21 women are shown in Table 2. The original nephropathies were glomerulophaty, 45%; reflux nephropathy, 31%; hypoplasia/dysplasia, 10%; and vascular nephropathy, 14%. When the nonparametric Kruskal-Wallis test was applied, the TC levels were significantly lower in hypoplasia/dysplasia group when compared with the other etiologies.

Nutritional status expressed by BMI in the beginning of the study showed 38% obesity, 12% overweight, and 50%

**Table 3. Habitual Intake Food in 42 Renal Pediatric Transplant Recipients**

| NCEP CT Categories | Acceptable | Risk | High | *P** |
|---|---|---|---|---|
| Total calories | 1527 ± 404 | 1635 ± 493 | 1592 ± 45 | NS |
| % RDA adecuation | 97 ± 30 | 111 ± 27 | 106 ± 28 | NS |
| Proteins (%) | 13.6 ± 3 | 15.7 ± 2.3 | 14 ± 5 | NS |
| Carbohydrates (%) | 55 ± 9 | 54.8 ± 4.6 | 53.6 ± 10.4 | NS |
| Lipids (%) | 31.5 ± 9.9 | 29.6 ± 8.6 | 32.2 ± 11.9 | NS |
| Saturated fat (%) | 9.6 ± 2.6 | 11.2 ± 4.6 | 8.7 ± 3.2 | NS |
| Monounsaturated fat (%) | 9 ± 3.5 | 9.2 ± 5.2 | 8.9 ± 4.3 | NS |
| Polyunsaturated fat (%) | 11 ± 6.4 | 10.5 ± 9 | 11.3 ± 6.6 | NS |
| P/S | 1.14 ± 0.6 | 0.83 ± 0.6 | 0.98 ± 0.6 | NS |
| Fiber (g/d) | 16.7 ± 12.3 | 14.5 ± 10.7 | 14.2 ± 8.3 | NS |

NCEP, National Cholesterol Education Program; TC, total cholesterol; NS, not significant.
Values are expressed as mean ± SD.
*ANOVA.

**Table 4. Lipid Profile in 42 Pediatric Renal Transplant Recipients**

| Category NCEP (mg/dL) | Average (mean ± SD) | Range |
|---|---|---|
| TC | 177.5 ± 44.2 | 92–308 |
| LDL-C | 105.3 ± 38.2 | 42–235 |
| HDL-C | 42.0 ± 12.5 | 17–68 |
| TG | 143.5 ± 79.3 | 51–400 |
| CT/HDL | 4.6 ± 1.7 | 2–10.7 |

normal. Hypercholesterolemic patients showed a higher BMI. Mean protein intake was 14 ± 3.7%, fats 31.1 ± 10.1%, and carbohydrates 54.6 ± 9.4%. When dietary energy intake, total calories, saturated fat, and polyunsaturated/saturated fat relation were compared according NCEP categories no significant differences were found (Table 3). Family history of hypetriglyceridemia was present in one girl who showed triglyceride concentrations above 95.

Twenty-two patients (50%) exhibited elevated serum TC; in 12 (29%), TC was higher than 200 mg/dL. Six patients (14%) had LDL-C levels higher than 130 mg/dL, and nine patients (21%) between 110 and 129 mg/dL (Table 4). Hypertriglyceridemia considered >95 by sex and age, was found in 50% of the patients, average 203.9 ± 73 mg/dL. When blood lipids were compared by NCEP categories, significant differences were found between the groups, as well as to risk cardiovascular disease according CT/HDL relation (Table 5).

Twenty-three patients had received prednisone daily at doses 0.14 ± 0.12 mg/kg and in the other 19, prednisone was administrated in alternate days 0.21 ± 0.08 mg/kg. The mean of cyclosporine A (CsA) doses was 5.5 ± 1.6 mg/kg/d and cyclosporine levels was 167.8 ± 53 $\mu$g/mL. Daily prednisone doses were associated with increasing TG levels (Fig 1); hypercolesterolemic patients showed higher levels of GA ($P = .02$) (Fig 2).

Posttransplant follow up was 2.7 years (range, 0.6 to 8.4 years) and 57% of patients received a kidney from a cadaveric donor. No significant differences between posttransplant follow up, donor graft group, and lipid profile was found.

Fifty percent of the patients presented hypertension. A direct correlation was observed between TC and systolic ($P = .04$) and diastolic blood pressure ($P = .03$). The mean GRF was 68.2 ± 17.9 mL/min (range, 26.4 to 90.0). The GRF was higher than 50 mL/min in 80% of the patients; no relation was found between lipid profile and GRF. Multivariate regression analysis showed that there was only a significant association between LDL-C concentration and BMI ($P = .02$) and LDL-C levels and diary prednisone doses ($P = .01$).

**Table 5. Changes in the Intake of Food in 12 Hypercholesterolemic Renal Pediatric Transplant Recipients Post-Low Cholesterol Diet**

| Intake | Before | After |
|---|---|---|
| %RDA adecuation of total calories | 117.1 ± 28.1 | 84.8 ± 11.2* |
| % AGS | 10.7 ± 4.5 | 6.6 ± 1.8** |
| P/S | 0.6 ± 0.3 | 2 ± 0.8*** |
| Cholesterol (mg/dL) | 188.5 ± 121.1 | 100.7 ± 73.4[&] |

*$P = .01$; **$P = .001$; ***$P = .0001$.
[&]Wilcoxon test.

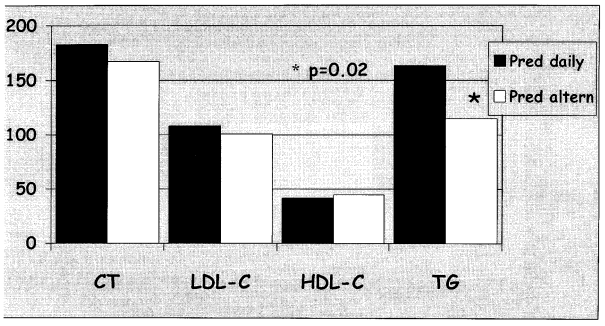


**Fig 1.** Steroid schedule and lipid profile.

Twenty-two patients met the hyperlipidemia criteria (9 boys, 13 girls), and only 12 of them (54%) decided to participate in dietary modification and completed the study. Five children lived far from the hospital and were excluded because it was difficult to get good compliance with treatment, and the other five were adolescents who were not interested in participating.

In this study all patients were on Step I Diet before the study was started, so they should be subjected to Step II Diet from the beginning. The best adherence to the diet was observed with relationship to the intake of cholesterol and the worse adherence registered was relationship to monounsaturated fat intake. No patient showed 100% of adherence to all the established modifications. Mean energy intake, total calories, percentage of saturated fatty acid, and intake of cholesterol diminished significantly during the intervention and the relationship polyunsaturated/saturated increased (Table 6).

A significant decrease in TC and LDL-C was observed after 12 weeks of diet modification ($P = .05$). Post-diet lipid profile at 4 and 12 weeks are shown in Table 7. Triglyceride and HDL-C concentrations were not modified by AHA Step II Diet (Fig 3). Neither body weight or BMI were modified by the diet.

## DISCUSSION

Cardiovascular disease is the leading cause of death worldwide among adults patients; hypertension and hyperlipidemia are the principal risk factors. It is believed that hyperlipidemia is a factor that contributes to the progression of human chronic renal failure.[12] The same circulating lipid abnormalities that have been implicated in the pathogenesis of systemic atherosclerosis are common in renal transplant recipients with chronic rejection.[13]

The NAPRTCS registry collected data from 130 centers on 4329 children reporting 6-year graft survival rates of

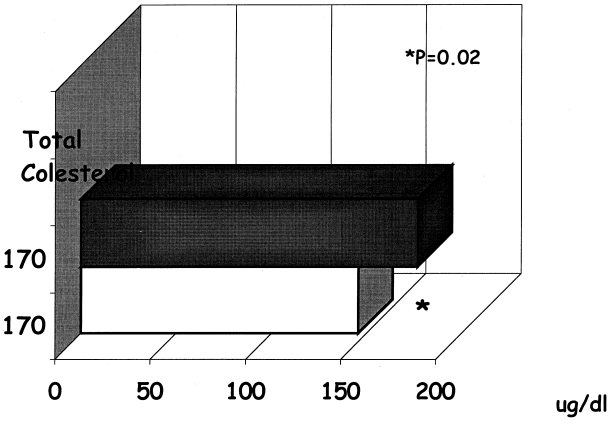


**Fig 2.** Cyclosporine levels and total cholesterol.

73% living recipients and 56% cadaver donors grafts.[3] As a result of improved outcomes in transplant survival, the natural history of lipid abnormalities has been studied in pediatric transplant population. Higher levels of total cholesterol were found in posttransplant immunosuppressed patients when lipid profile was compared with children who were not under immunosuppressive therapy. The authors suggest that despite significant reduction in the cyclosporine and prednisone doses posttransplantation, most of the children continue to have an abnormal lipid profile as compared to controls.[2] Similar attention to the high total cholesterol level 2 years posttransplant has previously been drawn by Ettenger.[14]

The results of the present study showed a high prevalence of combined hyperlipidemia as well as isolated hypercholesterolemia and hypertriglyceridemia, when it is compared with healthy Chilean children. Casanueva[15] reported a 10% of prevalence of hypercholesterolemia in urban children and 1.9% in rural children. Nutritional status expressed by BMI in the beginning of the study showed 38% obesity and 12% overweight. Hypercholesterolemic patients showed a tendency to have a higher BMI. Our findings were similar to those reported by Goldstein et al,[16] in 30 French transplanted children who showed 40% hyperlipidemia and 30% hypercholesterolemia and hypertriglyceridemia.

Although neither body weight nor BMI were modified by the diet, the mean energy intake, total calories, saturated fat, and cholesterol were significantly reduced post diet; the same was observed in the polyunsaturated/saturated fat relationship.

Daily prednisone doses were associated with increased concentrations of triglycerides in this study. Immunosuppressive therapy is clearly implicated in maintaining hypertriglyceridemia and in the development of hypercholesterolemia posttransplantation. A previous study of 25 pediatric dialysis patients reported higher triglyceride levels and, following transplantation, hypertriglyceridemia persist and hypercolesterolemia develops. Corticosteroids enhance peripheral resistance to the action of insulin impairing the clearance of triglycerides and hyperinsulinemia increased hepatic production of TG.[17]

A linear regression analysis model showed total cholesterol above 170 mg/dL was related to higher diastolic arterial pressure. Hypertension is one of the main risk factors for cardiovascular disease; when these risk factors occur in combination with hyperlipidemia and low serum HDL-C concentration, early cardiovascular disease is commonplace.

In our study, mean time of posttransplant follow up was 2.7 years and there was no correlation between years since transplant and hypercholesterolemia. Our findings suggest that dyslipidemic children are distributed over posttransplant time and the risk is not higher during the first posttransplant year as has been showed by Silverstein et al.[18] A 3-year follow up of creatinine clearence values showed an average of 68 mL/min per 1.73 $m^2$, according to a long-term estimate GRF, where an average loss of renal function of 5 mL/min/1.73 $m^2$ per year, was reported in transplanted patients.[19] GRF less than 50 mL/min/1.73 $m^2$ was not related to hypercholesterolemia in this group of patients, as has been reported.[20]

Correlation between CsA levels and hypercholesterolemia was shown in this study, where positive correlation showed up when the levels of CsA were related to TC concentrations. The mechanism by which CsA may potentiate lipid abnormalities induced by steroids has not been well elucidate. CsA is highly lipophilic and up to 80% of the drug is transported in plasma by binding to lipoproteins, particularly LDL-C. This binding results in impaired clearance of LDL-C from the circulation via cell-surface LDL receptors. Low levels of free CsA may lead to lesser immunosuppression and to explain at least some of the relationship between lipid levels and renal allograft rejection. In vitro experiments reveal an increase in the expression of class II antigens in monocytes induced by oxidized LDL-C. It is known that the expression of these antigens plays a pathogenic role in the induction of rejection. Mesangial cells can incorporate lipid material and receptors for oxidized LDL-C have been found in them. Oxidized

**Table 6. Lipid Profile by NCEP Total Cholesterol in 42 Pediatric Renal Transplant Recipients**

| Total Cholesterol | Acceptable ($n$ = 20) | Risk ($n$ = 10) | High ($n$ = 12) | $P$* |
|---|---|---|---|---|
| LDL-C (mg/dL) | 84 (76–109) | 112.5 (42–128) | 130 (81–235) | .0001 |
| HDL (mg/dL) | 34 (22–68) | 46.5 (17–62) | 44.5 (22–54) | .007 |
| TG (mg/dL) | 97.5 (80–308) | 130 (51–191) | 204 (109–400) | .023 |
| CT/HDL (mg/dL) | 3.9 (3–7.3) | 4.0 (2–7.9) | 4.9 (4–10.7) | .01 |

*Kruskal-Wallis test.

**Table 7. Modification of Lipid Profile in 12 Hypercholesterolemic Pediatric Renal Transplant Recipients After Low-Cholesterol Diet**

| Lipid Profile | Basal | 4 Weeks | 12 Weeks |
|---|---|---|---|
| TC (mg/dL) | 205.4 ± 28.4 | 193.6 ± 44.8 | 181.6 ± 32.5* |
| LDL-C (mg/dL) | 123.3 ± 30.5 | 118.1 ± 34.5 | 105.3 ± 22.4* |
| HDL-C (mg/dL) | 48.4 ± 10.6 | 43 ± 9.5 | 43.6 ± 14.6 |
| TG (mg/dL) | 175.3 ± 85.6 | 156.3 ± 80.5 | 161.5 ± 80.8 |
| TC/HDL-C (mg/dL) | 4.3 ± 1.4 | 4.6 ± 1.3 | 4.5 ± 1.2 |

Data are presented as mean ± SD.
*$P$ = .05, Student $t$ test.

LDL-C participates in the genesis of atherosclerosis through foam cell formation.[13] Lipid-lowering agents, in addition to the beneficial effects of the reduction in serum lipids, may influence important intracellular pathways that are involved in the inflammatory and fibrogenic responses, which are common components of many forms of progressive renal injury.[12]

Although diet is not an invasive intervention and it has few adverse effects, it was not accepted as an option of treatment in all of our patients. The argument was that they had been on a restricted diet for years, during dialysis therapy.

Depending on the degree of hyperlipidemia, AHA Step I or Step II Diet can be started immediately if the patient is already restricting his intake of saturated fatty acids to less than 10% of total calories or if the risk of cardiovascular disease is high. In this study, all patients were on Step I Diet before the study was started. Step II Diet showed a significant decrease in TC and LDL-C levels in our patients (11% and 14%, respectively). In adults, long-term studies Step II Diet decreased serum LDL-C concentration ranging from 8% to 15%. More restricted diet in fat than in Step II Diet, results in little additional reduction in serum LDL-C, rise serum triglyceride and lower serum HDL-C concentrations.[21,22] In this study Step II Diet was insufficient to decrease TC in 30% of the patients and failed to decrease LDL-C in 50% of the patients, serum TG concentration was not modificated by diet and serum HDL-C levels were a risk factor for cardiovascular disease.

Statins are structurally similar to hydroxymetylglutaryl-coenzyme A (HMG-CoA) a precursor of cholesterol, being competitive inhibitors of HMG-CoA reductase, the last regulated step in the synthesis of cholesterol. These drugs diminish serum LDL-C concentrations by upregulating LDL-receptor activity as well as reducing the entry of LDL into circulation. In adults the maximal reduction in serum LDL-C concentration induced by treatment with statin ranges from 24% to 60%.[12] Preliminary studies in pediatric patients have shown favorable results on hypercholesterolemia in nephrotic syndrome. No studies to date have been reported in hypercholesterolemic pediatric renal transplant patients, probably because the levels of cholesterol are not as high as in the nephrotic syndrome. The HMG-CoA are indicated when TC concentrations exceed 240 mg/dL and LDL-C concentrations are higher than 160 mg/dL. In our study, no patients presented these levels in the lipid profile after 12 weeks of diet. Other multicentre and prospective studies are necessary to solve hyperlipidemia in posttransplant pediatric recipients.

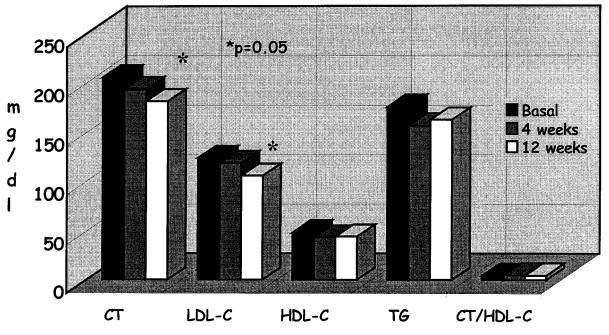


**Fig 3.** Modification of lipid profile in 12 pediatric renal transplant recipients after low-cholesterol diet.

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